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Attorney Docket No. 104685-140

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
BENNETT *et.al.*	)	Group Art Unit: 1644
	)	
Serial No.: 08/722,659	)	Examiner: M. Jamroz
	)	
Filed: September 27, 1996	)	
	)	

For: USE OF HEPARINASE TO DECREASE INFLAMMATORY RESPONSE

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION MAILED MAY 31, 2002

This paper is being filed in response to the outstanding Office Action mailed May 31, 2002 (Paper No. 35).

Formal Drawings

Applicants submit herewith four sheets of formal drawings for Figures 1, 6, 8, and 16. Entry of the drawings is respectfully requested.

Rejection under35 USC 102(e) or (f)

The Examiner has maintained the rejection of claims 1-7 and 18-19 under 35 U.S.C. 102(e) or (f) as allegedly being anticipated under U.S. Patent No. 5,997,863 ("the '863 patent"). Applicants respectfully traverse the rejection.

The '863 patent describes the distinction between wound healing and the reduction of inflammation: "The wound healing process is generally divided into three temporally

overlapping phases: inflammation, proliferation and remodeling." (Col. 2, lines 60-62.) Therefore, inflammation is one phase of wound healing. One having ordinary skill in the art would not expect that an agent that has been found to be useful for wound healing, which requires an increase in inflammation as one stage of the wound healing process, to also be useful to reduce inflammation. Accordingly, Applicants respectfully submit that the '863 patent does not teach each and every element of the claimed method of reducing inflammation because the '863 patent is directed only to the enhancement of wound healing, involving inflammation, prolifersation and remodeling.

Nevertheless, in order to expedite the prosecution of this application, Applicants submit herewith Rule 1.132 Declarations of Israel Vlodavsky and Richard Broughton, both named co-inventors on the '863 patent that are not named co-inventors of the instant application. The instant rejection relies on the disclosure of Example 8 to allege anticipation of the claims. Example 8 is entitled "Evaluation of Local Administration of Heparinase to Enhance Revascularization" and describes the administration of heparinase 1 in a rabbit hind limb ischemic model. Both Israel Vlodavsky and Richard Broughton identify that they were not involved in the animal model work described in Example 8 of the '863 patent involving the local administration of heparinase to enhance revascularization. In addition, these inventors point out that they believe that the named co-inventors, Bennett and Danagher, were the ones who contributed to the subject matter described in Example 8. Therefore, Applicants state that the subject matter relied upon in the '863 patent in the instant rejection is improper under 35 U.S.C. 102(e) as not being by "another."

Applicants further note that the Examiner has relied on other portions of the '863 patent, in particular, col. 6, lines 25-59 asserting that the '863 patent teaches that the administration of

heparinase releases heparin binding growth factors and degrading component of the extracellular matrix, facilitating the mobility of cytokines, for example. Specifically, the '863 patent states that:

> Glycosaminoglycan degrading enzymes from F. heparinum: heparinase 1 (EC 4.2.2.7), heparinase 2, heparinase 3 (EC 4.2.2.8), chondroitinase AC (EC 4.2.2.5) and chondroitinase B modulate the interactions involved in cell proliferation and migration by i) releasing heparin binding growth factors and molecules from the extracellular matrix, thereby increasing their availability to adjacent cells for the stimulation of proliferation and migration, ii) degrading components of the extracellular matrix, thereby facilitating the mobility of cytokines, chemoattractants and cells, iii) removing chondroitin sulfate from cell surfaces, thereby increasing access to cell surface receptors and iv) inhibiting the proliferative response of cells to growth factors by removing the heparan sulfate component of their growth factor receptor complex.

(Col. 6, lines 34-48.) However, Applicants submit that these stated "interactions involved in cell proliferation and migration" as stated in the '863 patent are directed to wound healing, not the reduction of inflammation. In fact, the elements of "i) releasing heparin binding growth factors and molecules from the extracellular matrix, thereby increasing their availability to adjacent cells for the stimulation of proliferation and migration," and "ii) degrading components of the extracellular matrix, thereby facilitating the mobility of cytokines, chemoattractants and cells" could arguably lead to inflammation. For example, as stated in the March 18, 2002 Response, inflammation requires involves, *inter alia*, the release of chemotactic factors and cytokines from the injured tissue and endothelial cells which line the blood vessels. The release of these humoral factors, triggers the increased expression of adhesion molecules (selectins, integrins) on the endothelial cell surface. Increased adhesion molecules on endothelium, along with chemokines, promote the activation of neutrophils, which adhere to endothelial cells and then migrate from blood into tissue and secrete proteolytic enzymes, cytokines, chemotactic factors, and oxygen radicals, which injure and kill cells composing the tissue. Therefore, the

"interactions" described in the '863 patent appear to promote inflammation, as a function of wound healing, instead of reducing inflammation.

Moreover, the above "interactions" also do not meet the recited claim element of decreasing neutrophil transmigration to decrease the localized inflammatory response. Instead, according to the above-recited '863 patent excerpt, the components of the extracellular matrix are degraded to facilitate mobility of cytokines, chemoattractants, and cells.

As such, Applicants respectfully submit that none of the portions relied upon in the '863 patent teach or describe the claimed method of decreasing the localized inflammatory responses arising from an ischemia/reperfusion injury in a tissue of a patient comprising intravascularly administering to a patient heparinase enzyme to decrease neutrophil transmigration through activated endothelium and basement membrane of said vasculature which decreases the localized inflammatory response arising from an ischemia/reperfusion injury.

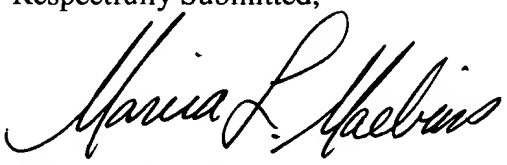
Withdrawal of the rejection is respectfully requested.

Conclusion

Applicants respectfully submit that this Application is in condition for allowance and the issuance of a Notice of Allowance is respectfully requested. In the event that the Examiner

disagrees, Applicants invite the Examiner to call the undersigned to discuss any outstanding issues.

Respectfully Submitted,



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